UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/797,690 | 03/10/2004 | Madhwa H.G. Raj | Raj 02M27.1 | 7199 |

25547 7590 03/22/2007

PATENT DEPARTMENT
TAYLOR, PORTER, BROOKS & PHILLIPS, L.L.P
P.O. BOX 2471
BATON ROUGE, LA 70821-2471

| EXAMINER | |
|---|---|
| DUFFY, BRADLEY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1643 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/22/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/797,690 | RAJ ET AL. | |
| | Examiner | Art Unit | |
| | Brad Duffy | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

## DETAILED ACTION

1. The election with traverse filed January 19, 2007, is acknowledged and has been entered.

Applicant has elected the invention of Group IV, claim 10. Furthermore, linking claims 9 and 22 will be examined with Group IV.

2. Claims 1-23 are pending in the application.

3. Claims 1-8, 11-21 and 23 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 19, 2007.

4. Claims 9-10 and 22 are under examination.

### *Election/Restrictions*

5. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed December 7, 2006, is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

The traversal is on the grounds that, "The Office has not carried its burden of showing that any of the 12 Groups are distinct from one another". Additionally the traversal argues that "the Office has not shown that there would be a serious burden in examining the Groups together" because, for example, "Groups IV through IX are identically classified, namely, in class 424, subclass 184.1".

Contrary to Applicant's assertions, the inventions are patentably distinct, each from the others, for the reasons set forth in the Office action mailed December 7, 2006.

To elaborate on this distinctness, for example, while Groups IV-VI are each drawn to methods of inhibiting prostate cancer in a mammal afflicted with prostate cancer, they each comprise immunizing the mammal against structurally and functionally distinct proteins (i.e., heterologous riboflavin carrier protein, heterologous folic acid binding protein or heterologous retinol binding protein, respectively). These proteins are patentably distinct at least because they bind structurally and functionally distinct vitamins, which the specification teaches starting on page 1. Furthermore, each protein comprises a structurally and functionally distinct amino acid sequence and would be expressed at different levels in normal and/or cancerous tissue. Thus, a method that targets just one protein to inhibit prostate cancer would be expected to have distinct criteria for success from any other. Additionally, it is noted that methods drawn to any particular combination would also be expected to have a distinct criteria for success from any other combination. Therefore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. See MPEP § 806.05(j). Thus, as elaborated in this example and for reasons of record as stated in the previous office action, each group is patentably distinct when compared to the others.

There would also be a serious burden to examine more than one of these processes for the reasons set forth in the Office action mailed December 7, 2006. Classification of subject matter is merely one indication of the burdensome nature of the search involved. In this case, the literature search is particularly relevant in this art and would not be co-extensive. Therefore, since these inventions have acquired a separate status in the art, the literature search is much more important in evaluating the burden of search that the classification of the invention. Clearly different searches and issues are raised in the examination of each group, which would create a burden on the Office.

Finally, Applicant has provided no evidence to establish why the groups are sufficiently related or why the requirement for restriction is improper. Clearly different searches and issues are raised in the examination of each group, which would create a burden on the Office. See MPEP 808.02.

For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

### *Information Disclosure Statement*

6. The references cited in the information disclosure statement filed on November 23, 2004, have been considered.

### *Oath*

7. The oath is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath is defective because: The oath indicates on page 2 that it was sworn to and subscribed before a Notary Public on June 6, 2004, however it appears that the inventor actually signed the oath on June 17, 2004 as this is the date next to the first inventor's signature. Furthermore, the second inventor did not date the oath when signing it. Therefore, it appears that this oath was not properly executed. A properly executed oath or declaration which complies with 37 CFR 1.67(a) and identifies the application by application number and filing date is required.

### *Specification*

8. The disclosure is objected to because of the following informalities:

(a) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such an improperly demarcated trademark appearing in the specification include Sepharose™ (see, e.g., page 10 and 12).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate

symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

(b) The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appear in the specification at, for example, paragraph [0071] and paragraph [0091] of the published application, U.S. Patent Application Publication No. 2004/0214788, which is viewable at http://appft1.uspto.gov/netahtml/PTO/search-bool.html.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

(c) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is indefinite because for reciting, "peptide subunits" and "peptide subunits may correspond to subunits of proteins" because the definition of "subunit" is unclear. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the specification must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). A subunit of a protein is generally considered a single unit of a multi-subunit protein (see definition of subunit provided as exhibit A). However, there is no evidence of record or in the art that riboflavin carrier protein is a multi-subunit protein. Therefore, is appears that applicant is contemplating a definition of "subunit" that is contrary to its ordinary meaning. However, in this case, because the specification does not clearly redefine the term "subunit" and riboflavin carrier protein does not comprise more that one unit, it is unclear what meaning of "subunit" is contemplated in this claim. Accordingly, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

Accordingly, this claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 9, 10 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims

in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In the instant case, the claims are directed to a method of immunizing a mammal afflicted with prostate cancer with a genus of "heterologous riboflavin carrier proteins", which the specification sets forth as a riboflavin carrier protein from one species being used to immunize a different species, which will then produce antibodies (see page 10). The specification further characterizes that said antibodies will not only bind the heterologous riboflavin carrier protein, but also the homologous riboflavin carrier protein (i.e., the actual protein expressed by the species immunized.)

Thus, the claims are broadly but reasonably directed to a genus of structurally and/or functionally disparate "heterologous riboflavin carrier proteins" from any species of organism (e.g., any vertebrate or invertebrate; any mammalian or non-mammalian animal, etc.).

In contrast to the breadth of the claims, as will be explained in further detail in the following paragraphs, the specification only adequately describes with the requisite particularity a chicken heterologous riboflavin carrier protein.

However, the specification does not describe heterologous riboflavin carrier proteins from any other species of organism.

Accordingly, because the claims are directed to a genus of "heterologous riboflavin carrier proteins" from any species, and there is no disclosure of any particularly identifying structural feature shared by these heterologous riboflavin carrier proteins, there is no disclosed correlation between any one particularly identifying structural feature shared by the members of the claimed genus and any one common particularly identifying functional feature (e.g., the ability to cause an immune response against the homologous riboflavin carrier protein). Consequently, the skilled artisan could not immediately envision, recognize or distinguish the members of the claimed genus of "heterologous riboflavin carrier proteins"; and therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

To further elaborate upon the reasons that the specification inadequately describes the claimed invention to satisfy the written description requirement, it is noted that numerous examples of antibodies exist that are not cross-reactive with an art-recognized heterologous protein. For example, Kliffen et al (Br J Ophthalmol, 84:1415-1419, 2000) teach a rabbit polyclonal antibody directed against human apo-E that does not react with mouse apo-E (see entire document, e.g., 1416, left column). Additionally, Rajavashisth et al (PNAS, 82:8085-8089) et al teach that the mouse apo-E polypeptide is approximately 70% homologous to human apo-E (see entire document, e.g. 8087, right column). Thus, one of skill in the art would not recognize that a heterologous protein from any species would necessarily create antibodies in a second mammalian species that would recognize the homologous protein in said second species.

Therefore, in order to adequately describe the genus of "heterologous riboflavin carrier proteins" to which the claims are directed, the specification would need to describe the structural features that are shared by the members of the genus that correlate with creating an immune response in a heterologous species that also creates antibodies to recognize homologous riboflavin carrier protein in that species. In this case, the specification has not disclosed any structural characteristics that are shared by members of this genus that would allow the skilled artisan to immediately envision, recognize or distinguish the members of the genus.

For example, Hamajima et al (Gene, 164:279-282, 1995) teach a turtle riboflavin-binding protein that is approximately 70% homologous to a chicken riboflavin-binding protein, which is also known as chicken "riboflavin carrier protein" (RCP) (see entire document, e.g., abstract)[1]. Given the teaching of Kliffen et al (supra) that a rabbit polyclonal antiserum directed against human apo-E did not cross-react with a heterologous protein (i.e. mouse apo-E) that was approximately 70% homologous, it is submitted that one of skill in the art would not immediately recognize or appreciate that the turtle riboflavin carrier protein, which is similarly only about 70% homologous to chicken RCP, might also be capable of eliciting an immune response in mammals that would create antibodies reactive against the homologous riboflavin carrier proteins in mammals afflicted with prostate cancer. Moreover, one of skill in the art would not immediately recognize or appreciate that such a protein that is only approximately 70% homologous would substantially share antigenic features (i.e., common epitopes) of any other riboflavin carrier protein, such as chicken RCP, so as to be commonly antigenic in mammals afflicted with prostate cancer and therapeutically effective in the practice of the claimed process.

Therefore, although the skilled artisan could potentially identify "heterologous riboflavin carrier proteins" encompassed by the claims by isolating heterologous riboflavin carrier proteins from other species and testing whether they could illicit an immune response that also produces antibodies to homologous riboflavin carrier proteins in mammals, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

[1] Subramanian et al (Biochim et Biophy Acta, 1429:74-82, 1998) teach "chicken riboflavin carrier protein" is also known as "chicken riboflavin binding protein" (see entire document, e.g., page 74, left column).

*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Applicant is reminded "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of "heterologous riboflavin carrier proteins" to which the claims are directed, and particularly members of the genus that are used effectively to achieve the claimed objective, because the structurally identifying features of "heterologous riboflavin carrier proteins" that would allow them to illicit an immune response that also identifies homologous riboflavin carrier proteins in mammals is missing from the specification. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of antibodies, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not

described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

In summary, the specification fails to describe at least a substantial number of "heterologous riboflavin carrier proteins". Moreover, the specification does not describe a correlation between any particularly identifying (i.e., substantial) structural feature that describes the presupposed representative species, which is shared by at least most of the other members of the genus, and any one particularly identifying functional feature also shared by at least most that may be attributed to the presence of the particularly identifying structural feature. Consequently, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the members of the claimed genus of "heterologous riboflavin carrier proteins" and therefore the supporting disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

13. Claims 9, 10 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The specification does not enable the use of a method of inhibiting prostate cancer in a mammal afflicted with prostate cancer, comprising immunizing said mammal against heterologous riboflavin carrier protein or immunizing said mammal against peptide subunits of heterologous riboflavin carrier protein.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claims are drawn to a method of inhibiting prostate cancer in a mammal afflicted with prostate cancer, comprising immunizing said mammal against heterologous riboflavin carrier protein or immunizing said mammal against peptide subunits of any riboflavin carrier protein. Since the term "inhibiting" is not explicitly defined in the specification, guidance as to the meaning and breadth of the term, as it is used in the context of the claims, is lacking; accordingly, "inhibiting" is broadly but reasonably interpreted as causing the effect of slowing disease progression or reversing disease progression.

The specification discloses that a rabbit polyclonal antibody generated against chicken riboflavin carrier protein can kill prostate cancer cell lines *in vitro* (see page 10, paragraph [0039]). The specification further discloses that tumor formation was inhibited in a mouse xenograft model system in three mice treated with a mixture of antibodies directed against riboflavin carrier protein, folic acid binding protein and retinol binding protein at the same time these mice where challenged with tumor cells (see page 11, paragraph [0041]). The specification does not disclose any working examples

of a model system for inhibiting prostate cancer in a mammal afflicted with prostate cancer using an antibody to riboflavin carrier protein, nor does it disclose any working examples for inhibiting prostate cancer in a mammal afflicted with cancer comprising immunizing said mammal with heterologous riboflavin carrier protein or a peptide subunit of any riboflavin carrier protein. Additionally, the specification does not provide any specific, non-general guidance on how to use a heterologous riboflavin carrier protein as an immunogen to inhibit prostate cancer in mammals afflicted with prostate cancer. Furthermore, at the time the instant application was filed, extrapolating *in vitro* cell line data and mouse xenograft model data to a cancer treatment was highly unpredictable in the art and it was well-known it the art that cancer vaccines were also highly unpredictable.

The state of the art was such that those of skill in the art readily recognized the unpredictability of extrapolating *in vitro* cell line data or mouse xenograft model data to human treatments, even when the extrapolation was from the same product tested *in vitro* or in the mouse tumor model to its use as a human tumor treatment. For example, Dennis (Nature, 442:739-741, August 2006) states "human cells are likely to behave differently in a mouse than in a human body, making results hard to interpret) (see page 739, middle column) and that "interactions between tumour cells and their neighbors are often lost in xenografts, because proteins from one species can't interact with their counterparts in the host" (see page 740, third column). Furthermore, Srivastava (Nature Immunology, 1(5):363-366, November 2000) teaches that "the human cancers that we aim to treat are well established and have taken their time getting there", while the mouse models used are often "established for anything from a few hours to less than a week before treatment" and that mouse models "must show some semblance to the human disease to be credible" (see page 365, right column). Finally, Zips et al (in vivo, 19:1-8, 2005) teach that "[u]nlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells", so predicting the effect of an anticancer agent *in vivo* based on *in vitro* data is not reliable (see page 3, right column).

Furthermore, the art recognizes that this unpredictably particularly applies to strategies based on immune responses, especially strategies drawn to cancer vaccines comprising immunizing a patient with a polypeptide. For example, Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) states "treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future" (see page 1354 lines 13-17). Further, DeGruijl T. D. et al (Nature Medicine, 5(10): 1124-1125, Oct. 1999) state that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. DeGruijl also states "precise correlates of clinical effects and immunological responses have been lacking" (see page 1124, left column).

In the instant case, the extrapolation required is from an antibody that causes cell death *in* vitro or a mixture of three antibodies (only one of which binds riboflavin carrier protein) that inhibits tumor *formation* in a mouse xenograft model system to a cancer vaccine that inhibits already *established* prostate cancer. One of skill in the art would not consider the *in vitro* data or the mouse xenograft model data to be credible models to enable a method of inhibiting prostate cancer using a cancer vaccine with heterologous riboflavin protein as the immunogen. For example, because the tumor was not established in the mouse xenograft model prior to treatment, it is highly unpredictable whether an antibody that specifically recognizes riboflavin carrier protein would be able to inhibit a tumor that was established, which compounds the unpredictability related to determining whether immunizing a mammal afflicted with prostate cancer with a heterologous riboflavin carrier protein would be able to inhibit prostate cancer.

Furthermore, as noted in the above rejection of the claims, Kliffen et al. (*supra*) teaches a rabbit polyclonal antibody directed against human apo-E that, which does not react with mouse apo-E; and so, inasmuch as the claims are directed to a process comprising the use of any "riboflavin carrier protein", which is isolated from virtually any species of organism, it is aptly noted that the skilled artisan cannot predict whether the

protein used will elicit an immune response in the mammal afflicted with prostate cancer, so as to achieve any therapeutic effect. An antiserum produced against a heterologous antigen that fails to recognize the homologous antigen expressed by prostate cancer cells of the mammal is not reasonably expected to inhibit the growth or progression of those cells. In this instance, absent sufficient guidance and direction, the selection of members of the genus of riboflavin carrier proteins that are useful in practicing the invention to achieve the claimed effect falls into the realm of undue and/or unreasonable experimentation since the effect of immunizing mammals using those many different proteins must first necessarily be determined by empirical methods alone.

Finally with particular regard to claim 22, which is directed to "peptide subunits" of a protein (i.e., riboflavin carrier protein), which is not known to comprise multiple subunits, it appears the amount of guidance and direction disclosed in the specification would not reasonably enable the skilled artisan to make the protein(s) to which the claims are directed; and accordingly, the claimed process could not be used without undue and/or unreasonable experimentation.

In view of the evidence of the lack of the predictability of the art to which the invention pertains, the lack of guidance and direction providing a specific and detailed description in applicant's specification of how to effectively practice the claimed method of inhibiting prostate cancer in a mammal afflicted with prostate cancer, comprising immunizing said mammal against heterologous riboflavin carrier protein or immunizing said mammal against peptide subunits of heterologous riboflavin carrier protein, and the absence of working examples, undue experimentation would be required to practice the claimed method of inhibiting prostate cancer to achieve the claimed effect.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the

claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

***Conclusion***

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

bd
March 12, 2007

STEPHEN RAWLINGS
PRIMARY EXAMINER
ART UNIT 1643

DRUG DISCOVERY & DEVELOPMENT





Search

Go

Search Tips

## Glossary

3 5 A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Search: Go

Word Definition Word & Definition

| | |
|---|---|
| **Sigma (S) factor (sigma subunit)** | A bacterial transcription initiation factor that promotes association of RNA polymerase to specific initiation sites. |
| **Subunit** | A single unit of a multi-subunit protein. |



Current Issu

keeping produ

Current Iss
Reader Se
Free Subsc

The Science

Waters Optin Columns: Enab Laboratory-Sca Waters OBD™
Ultra Fast Mu Genotyping, Ida
Innovations t and peoples' liv
Sigma Prese

Webcasts

Educationa

View Webca

Scale-up Lin
Performance, and configuring